A New Malondiamide Synthesis in Liquid Ammonia Alkylation of Malondiamide with Alkali Hydroxide

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Alkylation of Malondiamide with Alkali Hydroxide*

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Synopsis

Alkylation of malondiamide was achieved by the reaction between the active methylene group of malondiamide and alkyl halide after using alkali hydroxide in liquid ammonia as metalation reagent. The process was named as malondiamide synthesis with alkali hydroxide in liquid ammonia. As alkali hydroxides, lithium, sodium and potassium hydroxides were used. And benzylation, ethylation, propylation, and butylation of malondiamide were performed in liquid ammonia at room temperature, the yeild being 70~85 per cent.

For explanating the speciality of the new synthetic method, the authors have proposed the following hypothesis. Alkali hydroxide in liquid ammonia is in equilibrium with alkali amide and produced water is fixed by liquid ammonia as ammonium hydroxide. The following reaction formulas were assumed :

$$NaOH(\text{in } NH_3) + NH_3 \rightleftarrows NaNH_2 + H_2O(\text{in } NH_3)$$

$$H_2O(\text{in } NH_3) + NH_3 \rightarrow NH_4OH$$

$$CH_2\begin{matrix}CONH_2\\CONH_2\end{matrix} + NaNH_2 \rightleftarrows \left[CH\begin{matrix}CONH_2\\CONH_2\end{matrix}\right]^- Na^+ + NH_3$$

$$\left[CH\begin{matrix}CONH_2\\CONH_2\end{matrix}\right]^- + RX \rightarrow CHR\begin{matrix}CONH_2\\CONH_2\end{matrix} + X^-$$

I. Introduction

Malonic ester synthesis is a process to alkylate active methylene group of malondiethyl (MDE) with alkyl halide after performing metalation with alkali alcoholate in absolute alcohol.(1) Recently, the authors(2) have published malondiamide synthesis in liquid ammonia, in which metalation of malondiamide(MDA) was conducted with lithium, sodium and potassium metals or their amides in liquid ammonia and then alkylated in high yield. By further study, it was found that metalation of MDA with alkali hydroxide, LiOH, NaOH and KOH, though insoluble in liquid ammonia, was possible and alkali malondiamide thus obtained was alkylated with alkyl halides, producing alkyl malondiamide (R-MDE) in high yield just as the former two methods. This new method was then named as

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* Organic Synthetic Chemistry with Liquid Ammonia-Alkali Hydroxide. I, published in Japanese in J. Chem. Soc. Japan (Ind. Chem. Section) **60** (1957),

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(1) L. F. Fieser and M. Fieser, *Textbook of Organic Chemistry* Tokyo. (1952) 291.

(2) K. Shimo and R. Asami, J. Chem. Soc. Japan (Pure Chem. Section) **78** (1957) 798 ; Sci. Rep. RITU, A **9** (1957), 319.

malondiamide synthesis with alkali hydroxide in liquid ammonia It is promising from the industrial stand point that alkali hydroxides are used instead of metallic alkali. Formerly, it has not absolutely considered to utilize alkali hydroxides in organic synthesis, because they were insoluble in liquid ammonia. This work may therefore be a pioneerwork to utilize liquid ammonia-alkali hydroxide in organic synthesis.

It is impossible to try metal substitution with alkali hydroxide in the malonic ester synthesis above stated and also it is rather reverse reaction considering from metalation formula which will be stated later. It is therefore due to special behavior of alkali hydroxide in liquid ammonia that the reverse reaction smoothly proceeds by alkali hydroxide in liquid ammonia. The alkylation and its speciality will be described below.

II. Experimental method

1. Reaction vessel

As the experiments are performed at room temperature, a pressure-vessel should be used, which is shown in Fig. 1. Details of manipulation should be consulted with a reference book.(3)

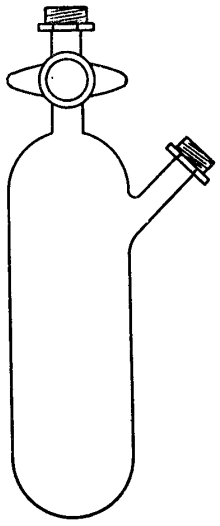


Fig. 1

2. Materials

MDE was obtained by distilling a commercial product under reduced pressure, b. p., 76~77°C/7 mmHg. MDA was prepared by treating MDE with ammonia, m. p., 169~171°C.

Sodium and potassium hydroxides were used after keeping tablets of the commercial products in a desiccator. Lithium hydroxide was dehydrated and used in a powdered state. Purities of the three hydroxides were determined by the acid titration: NaOH, 93%; KOH, 85%; and LiOH, 98%, and the rest was assumed to be water. Other basic substances of commercial products were used as they were.

Benzyl chloride was obtained by purifying a commercial product and the other alkyl halides were synthesized according to the ordinary method.

3. Metal substitution of MDA with alkali hydroxide and the reaction of which with alkyl halide

As alkali hydroxide is insoluble in liquid ammonia, the granular alkali hydroxide remains in a reaction vessel as it is, though mixed with liquid ammonia. But by adding more than equimolecular amount of MDA into the vessel, the alkali hydroxide begins to dissolve from the surface and a clear liquid ammonia solution results after 2 hours. The phenomenon is interesting and may be explained as

(3) Kôtarô Shimo, *Organic Chemistry of Liquid Ammonia*, (1956), Rika Book store., 3-41.

follow. The active methylene group of MDA reacts with alkali hydroxide, producing alkali malondiamide and water, and both products are soluble in liquid ammonia, at last Alkali hydroxide disappears. Then the product reacts with alkyl halide in liquid ammonia, producing R-MDA in high yield. The process is as follows. Granular or powdered alkali hydroxide is put in a reaction vessel with equimolecular amount of MDA and liquid ammonia. Metal substitution promptly proceeds, independently of standing or shaking the vessel. Even in case of standing the alkali is quickly consumed from the surface, resulting a clear liquid ammonia solution of alkali malondiamide after a few hours. By adding a small amount of phenolphthalein, the solution is tinged with red color. As stated in the former report,[2] an excess of equimolecular amount of alkyl halide is added to the solution under ordinary or elevated pressure, the reaction proceeds, precipitating insoluble alkali halide. On the completion of the reaction, color of the indicator fades to light pinc color. After standing for a definite hour, liquid ammonia is evaporated off and R-MDA is isolated from the residue

III. Experimental results

1. Benzylation of MDA and MDE

Five grams (0.05 mol) of MDA and 2.3 g (0.05 mol) of granular sodium hydroxide were taken into a reaction vessel, to which 60 cc of liquid ammonia were added and shaken at room temperature. After 2 hours; sodium hydroxide was dissolved, resulting a clear solution, to which 7 g (0.005 mol) of benzyl chloride were added and shaken. After about 1 hour, benzylation was almost completed, separating out insoluble sodium chloride. After one night's standing at room temperature, liquid ammonia was evaporated off, remaining white solid. After washing with water, the insoluble white solid was recrystallized from dilute alcohol, obtaining 6.4 g (yield 68%) of benzylmalondiamide, needles, m.p. 220~225°C, N, 14.64% (theo. 14.57), and 0.6 g of dibenzylmalondiamide, sandy, m.p. 194~196°C.

By the same process, 8 g (0.05 mol) of MDE, 2.3 g (0.05 mol) of sodium hydroxide and 7 g (0.06 mol) of benzylchloride gave solid product, from which 2.8 g (yield 30%) of benzylmalondiethyl were obtained by recrystallizing from dilute alcohol and 4.3 g (yield 39%) of benzylmalonoesteramide, m.p. 80~85°C, from ether.

As metalation reagent, except alkali hydroxides, calcium hydroxide, sodium carbonate or acetate was mixed with an equimolecular amount of MDA and shaken in liquid ammonia for a long time, but these bases did not dissolve. To the mixture benzyl chloride was added, resulting no benzyl compound. One part of MDA was recovered and benzyl chloride was recovered as benzylamine in case of calcium hydroxide or sodium cabonate was used, and as benzyl acetate in case of sodium acetate.

2. Ethylation of MDA

Five grams (0.05 mol) of MDA and 3.2 g (0.05 mol) of potassium hydroxide

were reacted in 50 cc of liquid ammonia, to which 6 g (0.06 mol) of ethyl bromide were added and shaken for 1 hour. After one night's shanding, liquid ammonia was evaporated off, resulting 3.8 g (71%) of ethylmalondiamide, plates, m. p. 207~211°C.

3. *n*-Butylation of MDA

Five grams (0.05 mol) of MDA and 1.3 g (0.05 mol) of powdered lithium hydroxide were reacted in 50 cc of liquid ammonia. After two hours' shaking, 8 g (0.06 mol) of *n*-butyl bromide were added to the solution. The product was washed with water and 6.0 g (77%) of *n*-butylmalondiamide were obtaned, needles, m. p. 192~195°C, N, 17.82% (17.69).

The above alkylation results were shown in Table 1 with the results obtained using alkali amides.

Table 1. (Alkylation of MDA using liquid ammonia-alkali hydroxide Reaction temperature: room temperature. Time for metalation: 2 hours, and for alkylation: 20 hours.)

MDA : M : RX = 1 : 1 : 1.1

MDA (g)	M	RX	R-MDA (g)	R-MDA (%)
5	LiOH	$C_6H_5CH_2Cl$	7.0	74
5	NaOH	〃	6.4	68
5	KOH	〃	6.7	71
5	$Ca(OH)_2$	〃	0	0
(MDE)				
8	NaOH	〃	2.8 R-MEA*	30
			4.3	39
MDA	$NaNH_2$	〃		75
〃	KNH_2	〃		79
5	LiOH	C_2H_5Br	4.0	75
5	NaOH	〃	4.6	86
5	KOH	〃	3.8	71
	KNH_2	〃		75
5	NaOH	*n*-C_3H_7Br	5.2	79
	KNH_2	〃		74
5	LiOH	*n*-C_4H_9Br	6.0	77
5	NaOH	〃	6.3	81
5	KOH	〃	5.3	70
	KNH_2			95

* R-MEA represent alkyl malonoesteramide.

IV. Discussion

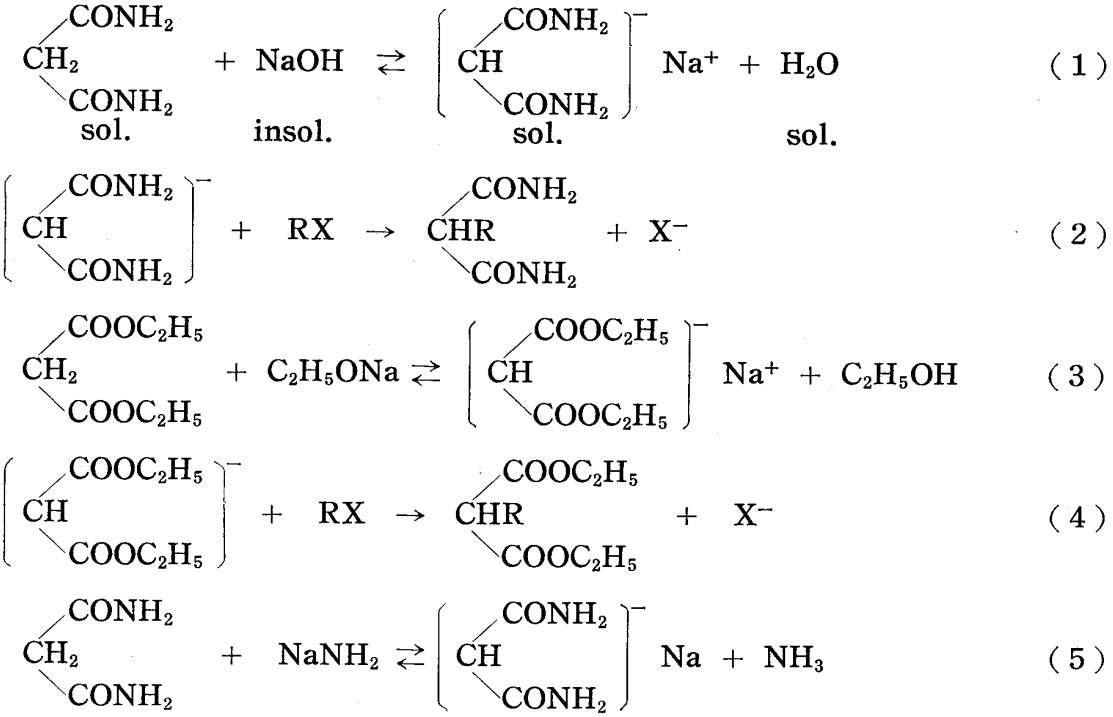
Metalation of MDA and MDE were performed in liquid ammonia and then they were alkylated with alkyl halides in liquid ammonia, resulting alkylmalondiamide. Their yields, as shown in Table 1 were high not less than those obtained in cases of alkali metals or alkali amides No special defference in yield due to the kind of alkali hydroxides was observed. Sodium hydroxide gave almost same yield with those by metallic alkali or alkali amides. As basic materials, except alkali hydroxide, calcium hydroxide, sodium carbouate and acetate were used for metalation reagent, but they remained insoluble and alkylation with alkyl halides

gave no R-MDA. It may be therefore concluded that this synthetic method is special to alkali hydroxide.

The reaction velocity of metalation may be qualitatively observed by the disappearing velocity of insoluble alkali hydroxide. In the present experimental condition, the disappearing velocity of alkali hydroxide is quick in the beginning, but becomes gradually slow afterwards. The hydroxide is however almost completely dissolved after 2 hours. The reaction velocity appearently becomes larger in the order: LiOH>NaOH>KOH. But their purity is as follows: LiOH, 98%; NaOH, 93%; and KOH, 85%, and the rest is assumed to be water. The larger the water content the slower the velocity. Also the velocity will be affected by their granular states The real metalation velocity will be therefore assumed to be almost same.

In the above alkylation, the effect of the kind of alkyl groups is almost same in case of liquid ammonia-malondiamide synthesis(2).

The synthetic method is divided into two stages, metalation and alkylation, expressing with (1) and (2) formulas, just the malonic ester synthesis with (3) and (4) formulas, and liquid ammonia-malondiamide synthesis with (5) and (2) formulas. Comparing the three synthetic methods with these formulas, it may be noticed that the alkali hydroxide method is differing from the other two in the formation of water in the metalation. Generally, such water constitute a big obstacle to the metalation of active methylene group. If alcohol contains water in the



malonic ester synthesis using alcohol as a solvent, the yield is decreased. The dehydration of the solvent alcohol is important in the synthesis.(4) Water in the

(4) *Organic Syntheses*, Coll. Vol. 1, p. 246.

system reversely acts to the metal substitution, because the hydrolysis of alkali malondiethyl (6) occurs and the reaction (3) goes back to left. The formula (6) shows that metalation becomes impossible when alkali hydroxide exists in alcohol.

$$\left[\begin{matrix} & \diagup COOC_2H_5 \\ CH & \\ & \diagdown COOC_2H_5 \end{matrix}\right]^- Na^+ + H_2O \rightarrow \begin{matrix} & \diagup COOC_2H_5 \\ CH_2 & \\ & \diagdown COOC_2H_5 \end{matrix} + NaOH \qquad (6)$$

According to the conception, the alkali hydroxide method (1) will not proceed to the right. But (1) proceeds to right in fact and metalation is completely conducted. The fact shows that the produced water in (1) will have no function shown in (6), by some contribution. In the reaction (1) and (6) appearently opposit, (6) reversely proceeds as (1), by replacing the solvent alcohol with liquid ammonia, and metalation of MDA and MDE are caused with alkali hydroxide. The authors have introduced a conception of the fixation of water shown by (7). Namely, when a small amount of water is present in a large amount of liquid ammonia, it is changed into NH_4OH, having no activity as water.

$$H_2O \text{ (in } NH_3) + NH_3 \longrightarrow NH_4OH \qquad (7)$$

Carbanion thus produced, according to (2) and (4) is alkylated by the nucleophilic substitution reaction S_N with alkyl halide as before.

The speciality of metalation due to alkali hydroxide has been thus explained. A problem is however remaining. Although it is considering that NaOH is dissociated into Na^+ and HO^- in (1), through the process, metalation is performed. Yet the authors assume the equilibrium state of NaOH with $NaNH_2^-$ in liquid ammonia shown by (8), and metalation is caused by alkali amide thus produced This conception is being confirmed by subsequent study.

$$NaOH \text{ (in } NH_3) + NH_3 \rightleftarrows NaNH_2 + H_2O \qquad (8)$$

Summarizing the above results, the speciality of malondiamide synthesis with alkali hydroxide in liquid ammonia is explained as follows. A minute of alkali hydroxide dissolved in liquid ammonia is in equilibrium with alkali amide, by which metalation of active methylene group is performed. On the other hand, water produced by the equilibrium is fixed with liquid ammonia to NH_4OH, by which water has no activity as water. The process is therefore reduced to malondiamide synthesis by alkali amide.